# **WEST Search History**

Hide Items Restore Clear Cancel

DATE: Tuesday, September 04, 2007

| Hide? | <u>Set</u><br>Name | Query   | <u>Hit</u><br>Count |
|-------|--------------------|---|---------------------|
|       | DB=PG              | PB,USPT; PLUR=YES; OP=ADJ   |                     |
| Γ     | L7                 | L4 and (@AD<20021024 or @RLAD<20020124 or @PRAD<20021024)                   | 2                   |
| Γ     | L6                 | L4 and (Zeldis.in. or Faleck.in. or Manning.in.)                            | 1                   |
| Г     | L5                 | L4 and (celgene.as.)  | 5                   |
| Г     | L4                 | L3 and ((complex regional pain syndrome) or (reflex sympathetic dystrophy)) | 15                  |
| Γ     | L3                 | 514/417.icls. or 514/417.ccls.  | 358                 |

END OF SEARCH HISTORY

| L1<br>L2<br>L3                   | FILE | 'REGISTRY' ENTERED AT 13:08:42 ON 04 SEP 2007 STRUCTURE UPLOADED 0 S L1 3 S L1 FAM FULL   |
|----------------------------------|------|---|
|                                  | FILE | 'STNGUIDE' ENTERED AT 13:09:42 ON 04 SEP 2007   |
| L4<br>L5<br>L6<br>L7<br>L8<br>L9 | FILE | 'HCAPLUS' ENTERED AT 13:11:42 ON 04 SEP 2007  17 S L3/THU  285 S (COMPLEX REGIONAL PAIN SYNDROME) OR (REFLEX SYMPATHETIC DYSTR  3827 S (NEUROPATHIC PAIN)  0 S L4 AND L5  1 S L4 AND L6  0 S L7 AND (PY<2003 OR AY<2003 OR PRY<2003)  0 S L8 AND (PY<2003 OR AY<2003 OR PRY<2003) |
|                                  | FILE | 'STNGUIDE' ENTERED AT 13:11:55 ON 04 SEP 2007   |
|                                  | FILE | 'HCAPLUS' ENTERED AT 13:12:09 ON 04 SEP 2007  |
|                                  | FILE | 'STNGUIDE' ENTERED AT 13:12:09 ON 04 SEP 2007   |
| L11                              | FILE | 'HCAPLUS' ENTERED AT 13:12:43 ON 04 SEP 2007<br>4 S L4 AND PAIN   |

=> file registry
COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE TOTAL ENTRY SESSION 0.21 0.21

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 3 SEP 2007 HIGHEST RN 945955-20-4 DICTIONARY FILE UPDATES: 3 SEP 2007 HIGHEST RN 945955-20-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

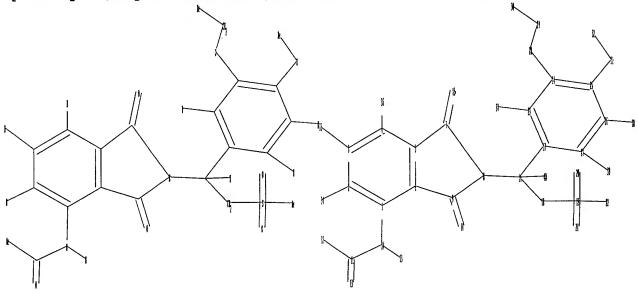
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>

Uploading C:\Program Files\Stnexp\Queries\10693722elected.str



chain nodes : 32 33 34 35 36 15 18 19 20 21 22 28 29 30 31 10 11 12 13 14 37 38 39 40 ring nodes : 25 26 27 9 17 23 24 chain bonds : 1-10 2-34 3-35 4-36 7-15 8-16 9-14 10-11 10-33 11-12 11-13 16-17 16-18 16-40 18-19 19-20 19-21 19-22 23-37 24-28 25-31 26-38 27-39 28-29 31-32

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 8-9 17-23 17-27 23-24 24-25 25-26 26-27

exact/norm bonds :

1-10 5-7 6-9 7-8 7-15 8-9 8-16 9-14 10-11 11-13 19-20 19-21 24-28 25-31

exact bonds :

2-34 3-35 4-36 10-33 11-12 16-17 16-18 16-40 18-19 19-22 23-37 26-38 27-39 28-29 29-30 31-32

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 17-23 17-27 23-24 24-25 25-26 26-27

## Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS

11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:CLASS

19:CLASS 20:CLASS

21:CLASS 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:CLASS 29:CLASS

30:CLASS 31:CLASS

32:CLASS 33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS

40:CLASS

## L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR

Structure attributes must be viewed using STN Express query preparation.

SAMPLE SEARCH INITIATED 13:09:21 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 5 TO ITERATE

100.0% PROCESSED 5 ITERATIONS 0 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 5 TO 234
PROJECTED ANSWERS: 0 TO 0

PROJECTED ANSWERS: 0 TO

L2 0 SEA SSS SAM L1

=> s l1 fam full FULL SEARCH INITIATED 13:09:29 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 66 TO ITERATE

100.0% PROCESSED 66 ITERATIONS 3 ANSWERS

SEARCH TIME: 00.00.01

L3 3 SEA FAM FUL L1

=> d 13 scan

L3 3 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN

IN Acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-

MF C22 H24 N2 O7 S

Absolute stereochemistry. Rotation (+).

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):3

L3 3 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN

IN Acetamide, N-[2-[(1R)-1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-

MF C22 H24 N2 O7 S

Absolute stereochemistry. Rotation (-).

# \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L3 3 ANSWERS REGISTRY COPYRIGHT 2007 ACS on STN

IN Acetamide, N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-

MF C22 H24 N2 O7 S

### \*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

#### ALL ANSWERS HAVE BEEN SCANNED

=> file stnguide
COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 68.15 68.36

FULL ESTIMATED COST

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Aug 31, 2007 (20070831/UP).

=> file hcaplus
COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 0.18 68.54

FULL ESTIMATED COST

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FILE COVERS 1907 - 4 Sep 2007 VOL 147 ISS 11 FILE LAST UPDATED: 3 Sep 2007 (20070903/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13/thu

17 L3 930166 THU/RL

L4 17 L3/THU

(L3 (L) THU/RL)

=> s (complex regional pain syndrome) or (reflex sympathetic dystrophy)

1359500 COMPLEX

69518 REGIONAL

53372 PAIN

130648 SYNDROME

127 COMPLEX REGIONAL PAIN SYNDROME

(COMPLEX (W) REGIONAL (W) PAIN (W) SYNDROME)

25547 REFLEX

40356 SYMPATHETIC

13389 DYSTROPHY

182 REFLEX SYMPATHETIC DYSTROPHY

(REFLEX (W) SYMPATHETIC (W) DYSTROPHY)

285 (COMPLEX REGIONAL PAIN SYNDROME) OR (REFLEX SYMPATHETIC DYSTROPH Y)

=> s (neuropathic pain)

4915 NEUROPATHIC

53372 PAIN

L6 3827 (NEUROPATHIC PAIN)

(NEUROPATHIC (W) PAIN)

=> s 14 and 15

L5

L7 0 L4 AND L5

=> s 14 and 16

L8 1 L4 AND L6

=> s 17 and (PY<2003 or AY<2003 or PRY<2003)

22887930 PY<2003 4458517 AY<2003 3937141 PRY<2003

L9 0 L7 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> s 18 and (PY<2003 or AY<2003 or PRY<2003)

22887930 PY<2003 4458517 AY<2003 3937141 PRY<2003

L10 0 L8 AND (PY<2003 OR AY<2003 OR PRY<2003)

=> file stnguide

COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 2.60 71.14

FULL ESTIMATED COST

FILE 'STNGUIDE' ENTERED AT 13:11:55 ON 04 SEP 2007 USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Aug 31, 2007 (20070831/UP).

=> d 18 ti abs bib
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

- L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2007 ACS on STN
- TI Composition comprising fumaric acid ester for treatment of an autoimmune and/or inflammatory disorder and related conditions
- AB The present invention relates to compns., kits and methods for administration of a first component of fumaric acid ester(s), or a pharmaceutically acceptable salt thereof, and a second component which is a substance that reduces or eliminates flushing.
- AN 2007:439616 HCAPLUS <<LOGINID::20070904>>
- DN 146:448435
- TI Composition comprising fumaric acid ester for treatment of an autoimmune and/or inflammatory disorder and related conditions
- IN Nilsson, Henrik
- PA Aditech Pharma AB, Swed.
- SO PCT Int. Appl., 48pp. CODEN: PIXXD2
- DT Patent
- LA English

FAN.CNT 3

|    |     |        |      |           |     |            |     |      |      | _   |       | - ~   |       |     |     |     |      |     |
|----|-----|--------|------|-----------|-----|------------|-----|------|------|-----|-------|-------|-------|-----|-----|-----|------|-----|
|    | PAT | CENT ! | NO.  |           |     | KINI       | )   | DATE |      | 1   | APPL. | ICAT. | I NOI | NO. |     | D   | ATE  |     |
|    |     |        |      | - <b></b> |     |            | -   |      |      |     |       |       |       |     |     |     |      |     |
| PI | WO  | 2007   | 0420 | 35        |     | A2         |     | 2007 | 0419 | 1   | VO 2  | 006-1 | DK56  | 3   |     | 20  | 0061 | 006 |
|    | WO  | 2007   | 0420 | 35        |     | <b>A</b> 3 |     | 2007 | 0614 |     |       |       |       |     |     |     |      |     |
|    |     | W:     | ΑE,  | AG,       | AL, | AM,        | AT, | AU,  | AZ,  | BA, | BB,   | BG,   | BR,   | BW, | BY, | ΒZ, | CA,  | CH, |
|    |     |        | CN,  | CO,       | CR, | CU,        | CZ, | DE,  | DK,  | DM, | DZ,   | EC,   | EE,   | EG, | ES, | FI, | GB,  | GD, |
|    |     |        | GE,  | GH,       | GM, | HN,        | HR, | HU,  | ID,  | IL, | IN,   | IS,   | JP,   | KE, | KG, | KM, | KN,  | ΚP, |
|    |     |        | KR,  | KZ,       | LA, | LC,        | LK, | LR,  | LS,  | LT, | LU,   | LV,   | LY,   | MA, | MD, | MG, | MK,  | MN, |
|    |     |        | MW,  | MX,       | MY, | MZ,        | NA, | NG,  | NI,  | NO, | ΝZ,   | OM,   | PG,   | PH, | PL, | PT, | RO,  | RS, |
|    |     |        | RU,  | SC,       | SD, | SE,        | SG, | SK,  | SL,  | SM, | sv,   | SY,   | ТJ,   | TM, | TN, | TR, | TT,  | TZ, |
|    |     |        | UA,  | ŪĠ,       | US, | UΖ,        | VC, | VN,  | ZA,  | ZM, | ZW    |       |       |     |     |     |      |     |
|    |     | RW:    | AT,  | BE,       | BG, | CH,        | CY, | CZ,  | DE,  | DK, | EE,   | ES,   | FI,   | FR, | GB, | GR, | ΗU,  | ΙE, |
|    |     |        | IS,  | IT,       | LT, | LU,        | LV, | MC,  | NL,  | PL, | PT,   | RO,   | SE,   | SI, | SK, | TR, | BF,  | ВJ, |
|    |     |        | CF,  | CG,       | CI, | CM,        | GA, | GN,  | GQ,  | GW, | ML,   | MR,   | NE,   | SN, | TD, | TG, | BW,  | GH, |
|    |     |        | GM,  | KE,       | LS, | MW,        | MZ, | NA,  | SD,  | SL, | SZ,   | TZ,   | ΰĠ,   | ZM, | ZW, | AM, | ΑZ,  | BY, |
|    |     |        |      |           |     |            |     |      |      |     |       |       |       |     |     |     |      |     |

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KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
                                                                                                                          WO 2005-DK648
                                                                                                                                                                             20051007
              WO 2006037342
                                                                                           20060413
                                                                        A2
             WO 2006037342
                                                                                          20060720
                                                                        Α3
                                   AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, VII, ZA, ZM, ZM
                        YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
                                    KG, KZ, MD, RU, TJ, TM
PRAI WO 2005-DK648
                                                                       Α
                                                                                           20051007
                                                                        Α
             DK 2006-511
                                                                                           20060407
             US 2006-511 A 20060407
US 2006-744458P P 20060407
DK 2004-1546 A 20041008
DK 2004-1736 A 20041110
DK 2005-211 A 20050211
DK 2005-419 A 20050323
US 2005-691513P P 20050616
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=> file hcaplus

COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION FULL ESTIMATED COST 0.06 76.69

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL
ENTRY SESSION

CA SUBSCRIBER PRICE

0.00 -0.78

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FILE COVERS 1907 - 4 Sep 2007 VOL 147 ISS 11 FILE LAST UPDATED: 3 Sep 2007 (20070903/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 14 and pain

53372 PAIN L11 4 L4 AND PAIN

=> file stnguide

COST IN U.S. DOLLARS
SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)
SINCE FILE TOTAL
ENTRY SESSION

-0.78

0.00

FILE 'STNGUIDE' ENTERED AT 13:12:44 ON 04 SEP 2007 USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Aug 31, 2007 (20070831/UP).

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=> d l11 1-4 ti
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

- L11 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
- TI Composition comprising fumaric acid ester for treatment of an autoimmune and/or inflammatory disorder and related conditions
- L11 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
- TI Preparation of substituted phenethyl sulfones and methods of reducing  $\mathtt{TNF}\alpha$  levels
- L11 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
- Use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity
- L11 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
- Use of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity

=> d l11 2-4 ti abs bib
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L11 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN

Ι

TI Preparation of substituted phenethyl sulfones and methods of reducing  $\mathtt{TNF}\alpha$  levels

GI

The title compds. I [Y = CO, CH2, SO2, CH2C(O); R1-R4 = H, halo, alkyl, alkoxy, etc.; R5, R6 = H, alkyl, alkoxy, CN, etc.; R7 = OH, alkyl, Ph, etc.], useful for reducing  $TNF\alpha$  levels and treating inflammatory and autoimmune diseases, were prepared and formulated. E.g., a 2-step synthesis of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindolin-1-one, starting from di-Me sulfone and 3-ethoxy-4-methoxybenzaldehyde, was given.

AN 2006:425851 HCAPLUS <<LOGINID::20070904>>

DN 147:189068

TI Preparation of substituted phenethyl sulfones and methods of reducing  $TNF\alpha$  levels

IN Man, Hon-Wah; Muller, George W.

PA Celgene Corporation, USA

SO Aust. Pat. Appl., 53 pp. CODEN: AUXXCM

DT Patent

LA English

FAN. CNT 3

| PAN. | PATENT NO.      | KIND | DATE     | APPLICATION NO. | DATE     |
|------|-----------------|------|----------|-----------------|----------|
|      |                 |      |          |                 |          |
| PI   | AU 2006200033   | Al   | 20060202 | AU 2006-200033  | 20060106 |
|      | AU 2003203681   | Al   | 20030703 | AU 2003-203681  | 20030409 |
| PRAI | AU 2003-203681  | A3   | 20030409 |                 |          |
|      | AU 2000-14472   | A3   | 19991019 |                 |          |
|      | WO 1999-US24376 | W    | 19991019 |                 |          |

L11 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN

I

Use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity

GI

The invention discloses stereomerically pure (S)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (+)-I, substantially free of its (-)-isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof. Methods of using and pharmaceutical compns. comprising (+)-I for treating and/or preventing disorders ameliorated by the reduction of levels of tumor necrosis factor α (TNF-α) or the inhibition of phosphodiesterase IV (PDE4) are also disclosed. Examples include the synthesis and resolution of (+)-I, thirteen bioassays, an aqueous solubility study, and three formulations. For instance, 3-nitrophthalic acid was hydrogenated using 10% Pd/C in EtOH to give the amine (84%), which was condensed with Ac2O to afford 3-acetamidophthalic anhydride (61%). Reaction of the phthalic anhydride with 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethylamine to give I (59%), followed by resolution with N-acetyl-L-leucine in MeOH provided (+)-I

(90% recovery, 98.4% ee). The latter inhibited LPS-induced TNF- $\alpha$ production by human whole blood and PDE4 activity with IC50 values of 294 nM and 73.5 nM, resp. (+)-I showed >500-fold to >40,000-fold selectivity for PDE4 over PDE1, PDE2, PDE3, PDE5, and PDE6. In addition, (+)-I suppressed LPS-induced lung neutrophilia in conscious ferrets with an ED50 of 0.8 mg/kg. Thus, (+)-I and its pharmaceutical compns. are useful for treating and/or preventing cancer, depression, and a variety of allergic, inflammatory, and autoimmune disorders (no data). 2003:777583 HCAPLUS <<LOGINID::20070904>>

AN

DN 139:296870

Use of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-TI acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity

Schafer, Peter H.; Muller, George W.; Man, Hon-Wah; Ge, Chuansheng IN

Celgene Corporation, USA PA

SO PCT Int. Appl., 57 pp.

CODEN: PIXXD2

DTPatent

LΑ English

FAN.CNT 3

|      | PATENT NO. |      |      |      |     | KIN | )   | DATE           |      |     | APPL | ICAT: | ION I | NO.  |     | Di       | ATE                  |     |  |  |
|------|------------|------|------|------|-----|-----|-----|----------------|------|-----|------|-------|-------|------|-----|----------|----------------------|-----|--|--|
|      |            |      |      |      | -   |     |     | WO 2003-US8738 |      |     |      |       |       |      |     |          |                      |     |  |  |
| PI   | WO         | 2003 |      |      |     |     |     |                |      |     |      |       |       |      |     |          |                      |     |  |  |
|      |            | W:   |      |      |     |     |     |                |      |     |      | BG,   |       |      |     |          |                      |     |  |  |
|      |            |      |      |      |     |     |     |                |      |     |      | EE,   |       |      |     |          |                      |     |  |  |
|      |            |      | GM,  | HR,  | HU, | ID, | IL, | IN,            | IS,  | JP, | KΕ,  | KG,   | ΚP,   | KR,  | KZ, | LC,      | LK,                  | LR, |  |  |
|      |            |      |      |      |     |     |     |                |      |     |      | MW,   |       |      |     |          |                      |     |  |  |
|      |            |      | PL,  | PT,  | RO, | RU, | SC, | SD,            | SE,  | SG, | SK,  | SL,   | ТJ,   | TM,  | TN, | TR,      | TT,                  | TZ, |  |  |
|      |            |      | ,    | ,    | ,   | ,   |     | VN,            |      | •   |      |       |       |      |     |          |                      |     |  |  |
|      |            | RW:  |      |      |     |     |     |                |      |     |      | TZ,   |       |      |     |          |                      |     |  |  |
|      |            |      | KG,  | ΚZ,  | MD, | RU, | ТJ, | TM,            | AT,  | BE, | BG,  | CH,   | CY,   | CZ,  | DE, | DK,      | EE,                  | ES, |  |  |
|      |            |      |      |      |     |     |     |                |      |     |      | NL,   |       |      |     |          |                      |     |  |  |
|      |            |      | BF,  | ВJ,  | CF, | CG, | CI, | CM,            | GA,  | GN, | GQ,  | GW,   | ML,   | MR,  | NE, | SN,      | TD,                  | TG  |  |  |
|      | CA         | 2479 | 666  |      |     | Al  |     |                |      |     |      |       |       |      |     |          | 20030320<br>20030320 |     |  |  |
|      | AU         | 2003 | 2247 | 29   |     | A1  |     |                |      |     |      |       |       |      |     |          |                      |     |  |  |
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Use of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity

The invention discloses stereomerically pure (R)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (-)-I, substantially free of its (+)-isomer, and prodrugs, metabolites, polymorphs, salts, solvates, hydrates, and clathrates thereof. Methods of using and pharmaceutical compns. comprising (-)-I for treating and/or preventing disorders ameliorated by the reduction of levels of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) or the inhibition of phosphodiesterase IV (PDE4) are also disclosed. Examples include the synthesis and resolution of (-)-I, seven bioassays, an aqueous solubility study, and three formulations.

Ι

For

instance, 3-nitrophthalic acid was hydrogenated using 10% Pd/C in EtOH to give the amine (84%), which was condensed with Ac2O to afford 3-acetamidophthalic anhydride (61%). Reaction of the phthalic anhydride with 1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethylamine to give I (59%), followed by resolution with N-acetyl-D-leucine in MeOH provided (-)-I (90% recovery, 98.4% ee). The latter inhibited LPS-induced TNF-a production by human whole blood and PDE4 activity with IC50 values of 371 nM and 611 nM, resp. (-)-I showed >45-fold to >39,000-fold selectivity for PDE4 over PDE1, PDE2, PDE3, PDE5, and PDE6. Thus, (-)-I and its pharmaceutical compns. are useful for treating and/or preventing cancer, depression, and a variety of allergic, inflammatory, and autoimmune disorders (no data).

AN 2003:777582 HCAPLUS <<LOGINID::20070904>>

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Use of (-)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and compositions thereof for inhibiting TNF- $\alpha$  production and PDE4 activity

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PA Celgene Corporation, USA

SO PCT Int. Appl., 49 pp.

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DT Patent

LA English

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